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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
|-----------------|-------------|----------------------|---------------------|------------------|
| 09/122,427 | 07/24/1998 | YIYU ZOU | UTSC584USC2 | 4389 |

7590 08/23/2004
PENNIE & EDMONDS LLP
1155 AVENUE OF THE AMERICAS
NEW YORK, NY 10036-2711

EXAMINER

KISHORE, GOLLAMUDI S

| ART UNIT | PAPER NUMBER |
|----------|--------------|
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1615

DATE MAILED: 08/23/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

09/122,427

Applicant(s)

ZOU ET AL.

Examiner

Gollamudi S Kishore, Ph.D

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☐ Responsive to communication(s) filed on 22 April 2004.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1, 4-9, 52-55, 57 and 59-86 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1, 4-9, 52-55, 57 and 59-86 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- 1) ☒ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)
Paper No(s)/Mail Date _____.
- 4) ☐ Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____.
- 5) ☐ Notice of Informal Patent Application (PTO-152)
- 6) ☐ Other: _____.

DETAILED ACTION

RCE filed on 4-22-04 is acknowledged.

Claims included in the prosecution are 1, 4-9, 52-55, 57 and 59-86.

Claim Rejections - 35 USC § 103

1. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

2. Claims 1, 4-9, 52-55, 57 and 59-86 are rejected under 35 U.S.C. 103(a) as being unpatentable over Mehta (4,950,432) or (5,811,119), further in view of Unger (5,585,112), Isliker (5,089,602), Hsu (5,653,996) individually or in combination.

Mehta (432) discloses preliposomal powders containing a drug and a mixture of phospholipids. The process of preparation involves dissolving the lipid in t-butanol-water mixture and lyophilization of the mixture into a preliposomal powder. Liposomes could be produced from this fine powder by simple

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incubation or suspension in an aqueous solution (note the abstract, columns 5-7, Examples and claims).

Mehta in 119 teaches a similar method which involves dissolving the lipid in t-butanol-water mixture and lyophilization of the mixture into a preliposomal powder. Liposomes could be produced from this fine powder by simple incubation or suspension in an aqueous solution (note the abstract and Example 1).

Mehta in these patents does not disclose the use of surfactants such as tweens in the preliposomal preparations.

Unger teaches that non-ionic detergents such as Tweens stabilize the liposome compositions (note col. 25, lines 38-48).

Islaker similarly teaches that Tweens could be used in liposome preparations; the liposome preparations are then lyophilized (Example 11).

Hsu teaches the use of Tweens in liposomal preparations (note col. 5, line 25 et seq.).

In essence, the secondary references all teach the routine practice in the art of the use of Tweens in liposomal preparations. Unger in particular teaches that these are liposomal stabilizers. The use of Tweens in the preparations of Mehta would have been obvious to one of ordinary skill in the art since these are stabilizers and routinely used in the art in liposomal preparations.

Applicant's arguments have been fully considered, but are not found to be persuasive. Applicant once again argues that none of the references cited by the examiner disclose or suggest a lyophilizate with a lipid and a surfactant, which

lyophilizate was made by lyophilizing the composition that did not contain liposomes at the time of lyophilization. The examiner disagrees. It is true that Mehta's compositions do not contain the surfactant during the lyophilization; but it is also true that Mehta's compositions also do not contain liposomes at the time of lyophilization. In response to applicant's arguments that in prior art, one must first make the liposomes and then use physical sizing methods, the examiner points out that a careful review of Mehta's examples in 432 indicates that no sizing of the liposomes was performed after the hydration of the preliposomal powders and applicant has not shown that Mehta's powders do not act in the same way as applicant's and therefore, applicant's argument that the inventor's discovery that submicron distribution can be achieved without having first to make liposomes and then to size them are not persuasive. In addition, the examiner points out that instant independent claims recite 'median diameter'. This indicates a broad range with upper limit in microns. Furthermore, the term, 'non-lipid surfactant' is a broad term, which includes numerous cationic, anionic, neutral and zwitterionic compounds and applicant, has not shown that any non-lipid surfactant would behave the same way. In fact, a careful review of instant specification indicates that according to applicants themselves, among the only two tested non-lipid surfactants, Tween 20 and Tween 80, Tween 80 did not decrease the median size of the liposomes and that both Tween 20 and Tween 80 are toxic (pages 26 and 27 of the specification). Applicants also appear to indicate on page 26, that the amount and type of surfactant is crucial since higher amounts of Tween 20 were found to disrupt the liposomes.

Applicant's arguments with regard to Unger that one of ordinary skill in the art would not be motivated to use sodium lauryl sulfate (SLS) are not found to be persuasive since instant claims do not recite any HLB criteria for the surfactant and the claim language 'non-lipid surfactant' does not exclude either cationic or anionic surfactants such as SLS taught by prior art.

Applicant's arguments with regard to Isliker and Hsu are not persuasive since these arguments once again are based on the physical sizing of the liposomes and as pointed out above, instant claim language does not exclude the physical sizing.

3. Claims 1, 4-9, 52-55, 57 and 59-86 are rejected under 35 U.S.C. 103(a) as being unpatentable over Mehta (4,950,432) or (5,811,119), further in view of JP 06-227966, JP 183953 individually or in combination or Vice versa: JP 06-227966 or JP 183953 in view of either Mehta (4,950,432) or (5,811,119).

Mehta (432) discloses preliposomal powders containing a drug and a mixture of phospholipids. The process of preparation involves dissolving the lipid in t-butanol-water mixture and lyophilization of the mixture into a preliposomal powder. Liposomes could be produced from this fine powder by simple incubation or suspension in an aqueous solution (note the abstract, columns 5-7, Examples and claims).

Mehta in 119 teaches a similar method which involves dissolving the lipid in t-butanol-water mixture and lyophilization of the mixture into a preliposomal powder. Liposomes could be produced from this fine powder by simple

incubation or suspension in an aqueous solution (note the abstract and Example 1).

Mehta in 432 or 119 does not disclose the use of surfactants such as tweens in the preliposomal preparations.

JP 227966 while disclosing a liposomal composition teaches that the inclusion of a nonionic surfactant to the membrane forming phospholipid makes the liposomes temperature-sensitive effectively releasing a medicine at 40-45 degrees. The surfactants disclosed are polyoxyethylene ethers and sorbitan esters. The amount of the surfactant is between 1 to 30 mole percent (note the abstract and pages 2-6 of the English translation).

JP 183953 discloses that inclusion of a nonionic surfactant in liposome compositions enables to produce uniform size liposomes, which are stable for a long time. The mole percentages of surfactant ranges from 5 to 95. The surfactants taught are tweens and Tritons (abstract and pages 1-5 of the English translation).

The inclusion of a nonionic surfactants in the proliposomal lyophilizates of Mehta would have been obvious to one of ordinary skill in the art since such an inclusion makes the liposomes temperature sensitive as taught by JP 227966 and enables one to produce uniform size liposomes which are stable for a long time as taught by JP 183953. Alternately, to lyophilize the liposomes of JP 227966 or JP 183953 would have been obvious to one of ordinary skill in the art since Mehta teaches the feasibility of preparing preliposomal lyophilizates for the subsequent preparation of liposomes upon the addition of an aqueous medium


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and one of ordinary skill in the art would be motivated to use Mehta's method with a reasonable expectation of success.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Gollamudi S Kishore, Ph.D whose telephone number is (571) 272-0598. The examiner can normally be reached on 6:30 AM-4 PM, alternate Friday off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Thurman K Page can be reached on (571) 272-0602. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).


Gollamudi S Kishore, Ph.D
Primary Examiner
Art Unit 1615

GSK